

REMARKS

Claims 1-46 were originally presented for examination.

In the first Office Action, mailed May 29, 2009, restriction was required between the following respective inventions:

Group I. claims 1-7 drawn to a first process comprising reacting a substrate with a biological catalyst in a hydrofluorocarbon in the presence of water.

Group II. claims 8-18 drawn to a second process comprising reacting a racemic mixture with a biological catalyst in a hydrofluorocarbon.

Group III. claims 19-29 drawn to a third process comprising reacting a meso compound to prepare a particular enantiomer with a biological catalyst in a hydrofluorocarbon.

Group IV. claims 30-46 drawn to a fourth process comprising reacting a prochiral compound with a biological catalyst in a hydrofluorocarbon.

Further, if Group I was elected, an additional species election of either protease or lipase from claim 4 was required.

In response to that first Office Action, applicants elected the Group I invention, claims 1-7, and the lipase species.

In the second Office Action, mailed August 28, 2009, the following rejections were stated by the Examiner:

1. Claims 1-7 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-37 of the assignee's copending application Serial No. 12/297,024;
2. Claims 1 and 7 were rejected as indefinite under 35 U.S.C. §112 for containing the term "biological catalyst";
3. Claim 5 was rejected as indefinite under 35 U.S.C. §112 for stating "that the enzyme is part of a whole cell structure";
4. Claims 1-3, 5 and 7 were rejected as lacking novelty under 35 U.S.C. §102(b) over WO 99/13098;
5. Claims 1-4 and 7 were rejected as obvious under 35 U.S.C. §103(a) over WO 98/42687 in view of the BEIER et al. publication;

6. Claim 6 was rejected as obvious under 35 U.S.C. §103(a) over WO 98/42687 in view of the BEIER publication, and further in view of the JANDA et al. publication;
7. Claims 1-5 and 7 were rejected as obvious under 35 U.S.C. §103(a) over WO 99/13098 in view of the SMIDT et al. publication;
8. Claim 6 was rejected as obvious under 35 U.S.C. §103(a) over WO 99/13098 in view of the SMIDT et al. and JANDA publications;
9. Claims 1-5 and 7 were rejected as obvious under 35 U.S.C. §103(a) over BLANCH et al. (4,925,790) in view of the FERRABOSCHI et al. publication; and
10. Claim 6 was rejected as obvious under 35 U.S.C. §103(a) over BLANCH et al. in view of the FERRABOSCHI and JANDA publications.

WO 98/42687 and WO 99/13098 were both cited in the PCT search results and were cited by applicants in an Information Disclosure Statement in the present application.

The BEIER et al., JANDA et al., SMIDT et al. and FERRABOSCHI publications and the BLANCH et al. patent were cited for the first time by the Examiner in the last Office Action.

As to the obvious-type double patenting rejection over claims 1-37 of applicants' assignees' later filed application Serial No. 12/297,024, it is respectfully submitted that the claims in the present application are patentably distinct from the claims in the cited application and vice versa and are not coextensive or overlapping in scope.

In the present application claim 1 requires that the process to be "**conducted in the presence of water at a level which is less than that required for the water to form a separate aqueous phase in the reaction system.**" That feature is not required, disclosed or claimed in co-pending application Serial No. 12/297,024.

Also, the claims of application Serial No. 12/297,024 require a process using a racemisation catalyst and another biological catalyst, in which a first enantiomeric compound is converted to a second enantiomeric compound by the racemisation catalyst, with the resulting second enantiomeric compound reacting in the presence of the biological catalyst in a third compound. In other words, the claims of co-pending application Serial No. 12/297,024 require the additional presence of a first enantiomeric compound and a racemisation catalyst in order to perform the required racemisation step. **No such features or steps are required or claimed in the present application.**

Accordingly, applicants respectfully submit that the claims on the two applications are clearly patentably distinct from each other and are not coextensive or overlapping in scope.

Therefore, it is respectfully requested that the double patenting rejection be reconsidered and withdrawn.

As to the indefiniteness rejection under 35 U.S.C. §112 of claims 1 and 7 on the basis of the words “biological catalyst”, it is respectfully submitted that the words are perfectly clear. In that regard attention is directed to the specification, page 9, which among other things states at lines 1-6:

The process of the present invention is conducted in the presence of a biological catalyst. **By a “biological catalyst”, we mean** a catalyst that can be found in biological tissues or systems. Particular biological catalysts for use in the process of the invention are the enzymes and abzymes. The biological catalyst must, of course, be capable of catalyzing a stereo-selective conversion of the substrate into the second compound. (emphasis added)

As to the indefiniteness rejection under 35 U.S.C. §112 of claim 5 for containing the language “that the enzyme is part of a whole cell structure”, it is also respectfully submitted that the language is perfectly clear. In that regard, attention is directed to the specification, page 10, which among other things at lines 3-10 specifically states:

Alternatively, the enzymes **may be part of a whole cell culture such as** a live cell culture, e.g. Lactobacillus acidophilus, a resting cell culture, e.g. dried baker’s yeast which can be activated by warm water or a non-viable cell culture which contains the enzyme and the required cofactor(s), e.g. dead yeast. The whole cell culture containing the enzyme will usually be immobilized on a solid, insoluble matrix, for example by physical absorption or bonding, using standard literature processes. The matrices discussed above may be used for this purpose. (emphasis added)

Accordingly, it is respectfully submitted that the language to which objection has been taken in claims 1, 5 and 7 is specifically and expressly defined in the specification and is therefore definite. Accordingly, it is requested that the indefiniteness rejections under 35 U.S.C. §112 of claims 1, 5 and 7 be reconsidered and withdrawn for the above reasons.

It is also respectfully requested that the rejections of the claims under 35 U.S.C. §§102 and 103 be reconsidered and withdrawn for the reasons to follow.

With regard to WO 99/13098, the saturation level for water in 1,1,1,2-tetrafluoroethane (Phytosol A or R-134a) is between 1000ppm and 2000ppm (0.1% to 0.2%) at 20°C to 40°C. None of the examples presented in WO 99/13098 has a quantity of water present that is below the saturation level for water at the temperatures of the examples. In Example 1 of WO 99/13098 100g of water is used in conjunction with between 1kg and 2kg of R-134a, corresponding to water levels of between 5% and 10%. These levels are between one and two orders of magnitude **greater** than the saturation level of water in R-134a. In addition, these ratios do not take into consideration the volumes of water added in the form of the aqueous sodium hydroxide solution, comprising approximately a further 90 ml of water. Even in Example 2, which is a more concentrated "slurry" reaction process, a water level of around 2% in R-134a was used, again neglecting the additional 100 ml or so of aqueous sodium hydroxide added.

Clearly, the solvent mixture used in all of the examples of WO 99/13098 is a two-phase mixture comprising an aqueous phase and a separate non-aqueous phase. In none of the examples is a hydrofluorocarbon solvent used in the absence of free-phase water. This is completely consistent with the general teaching provided by WO 99/13098 where at page 5, lines 5-14, the preferred ratios of non-aqueous solvent to water are discussed. The most preferred range of ratios is from 2:1 to 20:1 non-aqueous: water and certainly below 100:1 non-aqueous:water. Even the highest ratio (100:1 or approximately 1% water) is well beyond the saturation limit of water in R-134a (1000ppm to 2000ppm), the preferred non-aqueous solvent of WO 99/13098.

Accordingly, WO 99/13098 fails to disclose or suggest the process claimed in claim 1 "**which is conducted in the presence of water at a level which is less than that required for the water to form a separate aqueous phase in the reaction system.**"

Further, there is no evidence in WO 99/13098 that the enzymes were actually functioning within the non-aqueous solvent phase. It seems that the benefits of having a two-phase solvent mixture resulted from product partitioning into the separate non-aqueous counterphase, thus reducing the magnitude of enzymic product inhibition.

WO 98/42687 mentions trifluoromethane as the only hydrofluorocarbon solvent within a group of 29 or so halogenated solvents which themselves are only a small part of the dozens of listed solvents that may be used in that invention. The choice of solvents available is "any

solvent which is substantially non-reactive". WO 98/42687 provides no teaching of the use of a hydrofluorocarbon in preference to any of the numerous other solvents said to be suitable.

Biphasic solvent systems are also envisaged (page 25, line 15). Water and mixtures of water and organic solvents are preferred (page 30 lines 7-15), and where a water/organic mixture is used, the organic solvent is within the range of 0-95%. Accordingly, WO 98/42687 teaches towards a minimum of 5% water content in the solvent, which as discussed above, will be above the saturation level for water in the hydrofluorocarbons. If the skilled person were to take the teaching of WO 98/42687 towards the use of a hydrofluorocarbon solvent, it would most likely result in the biphasic combination described in WO 98/42687. Again, this is contrary to the process claimed in claim 1 "**which is conducted in the presence of water at a level which is less than that required for the water to form a separate aqueous phase in the reaction system.**"

BLANCH et al. is directed to enzymatic processes in supercritical fluids. At column 1, lines 28-46, the advantages of supercritical fluid solvents over liquid solvents in terms of mass-transfer and solubility are discussed. At column 2, lines 42-49 it is stated that reaction substrates are significantly more soluble in the supercritical fluid than in aqueous solutions or in organic aqueous liquid mixtures. All of the examples in BLANCH et al. make use of supercritical carbon dioxide as the solvent. Whilst the hydrofluorocarbon trifluoromethane is mentioned, it is simply one of a number of possible fluids (column 2, lines 60-63) that may be used in the supercritical state, all of which have relatively low critical temperatures and which are common supercritical fluids.

There is no disclosure or suggestion in BLANCH et al. of the use of liquid solvents, yet alone liquid hydrofluorocarbon solvents. Instead, the teaching of BLANCH et al. is exclusively away from the use of liquid solvents and towards the use of supercritical solvents, and in particular the use of supercritical carbon dioxide (column 3, line 16 and the examples).

BEIER et al. describes enzymic processes conducted in a liquid mixture of perfluorocarbon and hydrocarbon liquids at a temperature such that the two liquids form a single liquid phase. When cooled, the perfluorocarbon/hydrocarbon solvent separates into its two liquid phases, allowing highly fluorinated substrates or products to be recovered by partitioning into the perfluorocarbon phase. BEIER et al. describes the use of a hexane/perfluorohexane solvent system for the enzymic (trans)esterification of 1H,1H,2H,2H-perfluorodecanol with the

product fluorinated esters being partitioned into the perfluorohexane phase for subsequent recovery.

Accordingly, BEIER et al. is focused specifically on the use of perfluorinated solvent phase for the partitioning of highly fluorinated substrates or products from the reaction in a hydrocarbon/perfluorocarbon reaction medium. BEIER et al. is directed toward the use of highly fluorinated species to promote partitioning into the perfluorinated phase post-reaction. BEIER et al. is silent on the use of hydrofluorocarbon solvents, and in fact teaches away from their use at page 1680 where in conjunction with footnote 6 it is stated that:

The more polar the solvent, then the greater its ability to strip the 'essential water' from the surface of the protein and therefore hexane has emerged as a widely used solvent for such reactions

From the inevitable presence of highly polarized C-H bonds, the hydrofluorocarbons are more polar than the hydrocarbons or the perfluorocarbons used in BEIER et al. The skilled person would find no teaching in BEIER et al. to use hydrofluorocarbons for which another suitable counter-phase fluid would need to be found in order to effect the phase partitioning taught by BEIER et al.

Further, since the BEIER et al. process relies on the presence of two liquid phases for the partitioning process, the skilled person would have no motivation to look to use the supercritical fluids of BLANCH et al., let alone a supercritical hydrofluorocarbon.

Taken either alone or in combination, BEIER et al. and BLANCH et al. provide no teaching of the use of hydrofluorocarbon liquids as in the present claimed invention.

JANDA et al. provides no disclosure or suggestion that abzymes may be used in hydrofluorocarbon solvent systems. If the teaching of BLANCH et al. were followed with JANDA et al. providing the replacement of a lipase by an abzyme, then the skilled person would be guided to use a supercritical fluid, particularly carbon dioxide and away from the use of the liquid hydrofluorocarbon solvents of the present claimed invention.

At page 437, JANDA et al. describes the common general knowledge that "lipases are particularly effective on substrates at the interface between water and an immiscible organic phase". This is a clear teaching away from the use of water at levels below that of saturation as in the present claimed invention. If, for some unknown reason, the skilled person could make the leap from JANDA et al. toward using a hydrofluorocarbon solvent rather than the more usual

hydrocarbons, such as hexane, it would arguably be towards the use of the hydrofluorocarbon in a two-phase system as described in WO 99/13098 and not to the use of a hydrofluorocarbon with a water level below that of saturation as in the present claimed invention.

SMIDT et al. discloses the use of lipase for the enantioselective production of chiral amines. All of the enzymic hydrolytic reactions in SMIDT et al. were conducted in aqueous solution. Table 1 of SMIDT et al. shows that the addition of polar non-aqueous solvents resulted in a “drastic loss of enzyme activity”. The skilled person looking to synthesize chiral amines with high enantioselectivity would have no motivation to move away from the aqueous reaction medium of SMIDT et al., and if they did, it would most likely be toward the more conventional separate hydrocarbon/water biphasic system described in JANDA et al. rather than to make use of the relatively polar hydrofluorocarbon solvents. If they did decide to utilize a hydrofluorocarbon solvent, it would likely be in a biphasic manner as taught in WO 99/13098, not in the single-phase hydrofluorocarbon solvent systems of the present claimed invention.

Finally FERRABOSCHI et al. describes the use of a 1:2 liquid mixture of chloroform and tetrahydrofuran. FERRABOSCHI et al. provides no teaching or motivation to make use of a hydrofluorocarbon solvent as in the present invention. And, if they were somehow motivated to take the teaching of BLANCH et al. into consideration, they would be led toward the use of a supercritical solvent, particularly carbon dioxide, given the relatively low polarity of the species under consideration in FERRABOSCHI et al. The skilled person would have no reason to use the solvent systems of the present claimed invention.

On the last page of the last Office Action, applicants were requested to provide a list of all copending applications that set forth similar subject matter to the present claims. Applicants are not aware of any such copending U.S. applications other than Serial No. 12/297,024 which is addressed and argued hereinabove.

For the above reasons, it is respectfully submitted that all of the elected claims remaining

in the application, namely claims 1-7, are in condition for allowance. Accordingly, favorable reconsideration and allowance of the application are requested.

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Respectfully submitted,

  
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